

WHAT IS CLAIMED IS:

1. A method of determining a level of one or more disease states in a subject, said method comprising determining, for  
5 each of said disease states, an interpolated response profile, from interpolated perturbation response profiles correlated to levels of each of said disease states, for which similarity is greatest between a diagnostic profile and said one or a combination of said determined interpolated  
10 response profiles, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in one or more cells of said subject, and wherein said interpolated response profiles are the products of a method comprising  
15 (i) providing response profiles of one or more cells of one or more analogous subjects for each of said disease states wherein said response profiles are obtained by measuring a second plurality of cellular constituents in said cells of said one or  
20 more analogous subjects at a plurality of levels for each of said disease states, and  
(ii) interpolating said response profiles so that a response profile may be extracted over a range of levels for each of said disease states,  
25 wherein the level of each disease state correlated to each determined interpolated response profile indicates said levels of said disease states.
2. The method of claim 1 wherein the level of a single  
30 disease state is determined.
3. The method of claim 1 wherein the interpolated perturbation response profiles are correlated to levels of

each of said disease states by calibrating the interpolated response profiles to one or more clinical effects.

4. The method of claim 1 wherein one or more of said  
5 disease states are associated with a genetic mutation.

5. The method of claim 4 wherein said genetic mutation is in a coding region.

10 6. The method of claim 4 wherein said genetic mutation is a heterozygous mutation.

7. A method of determining a level of effect of one or more therapies upon a subject having a disease state, said method  
15 comprising determining, for each of said therapies, an interpolated response profile, from interpolated perturbation response profiles correlated to levels of effect of each of said therapies, for which similarity is greatest between a diagnostic profile and said one or a combination of said  
20 determined interpolated response profiles, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in one or more cells of said subject, and wherein said interpolated response profiles are the products of a method comprising:

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(i) providing response profiles of one or more cells of one or more analogous subjects for each of said therapies wherein said response profiles are obtained by measuring a second  
30 plurality of cellular constituents in said cells of said one or more analogous subjects at a plurality of levels of effect for each of said therapies, and

(ii) interpolating said response profiles so that a response profile may be extracted over a range of levels for each of said therapies,

5 wherein the level of effect of each therapy correlated to each determined interpolated response profile indicates said levels of effect of said therapies.

8. The method of claim 7 wherein the level of effect of a  
10 single therapy is determined.

9. The method of claim 7 wherein the interpolated  
perturbation response profiles are correlated to levels of  
effect of each of said therapies by calibrating the  
15 interpolated response profiles to one or more clinical  
effects.

10. The method of claim 9 wherein the one or more drug  
therapies are adjusted until the diagnostic profile matches  
20 the profile obtained in the calibrated perturbation response  
profiles at a desired level of the one or more clinical  
effects.

11. The method of claim 7 wherein one or more of said  
25 therapies comprise treatment with a drug.

12. The method of claim 11 wherein said drug increases the  
activity of a protein.

30 13. The method of claim 11 wherein said drug decreases the  
activity of a protein.

14. The method of claim 7 wherein said effect of at least  
one of said one or more therapies is a beneficial effect.

15. The method of claim 7 wherein said effect of at least one of said one or more therapies is an adverse effect.

16. The method of claim 15 wherein said adverse effect is a  
5 toxic effect.

17. The method of claim 1 or 7 wherein said interpolating comprises approximating by a sum of spline functions.

10 18. The method of claim 1 or 7 wherein said interpolating comprises approximating by a Hill function.

19. The method of claim 1 or 7 wherein said combination of said determined interpolated response profiles is the sum of  
15 said determined interpolated response profiles.

20. The method of claim 1 wherein said determined level of said one or more disease states is a level which minimizes the value of an objective function of the difference between  
20 said diagnostic profile and the perturbation response profile extracted from said perturbation response curves for each said determined level of said one or more disease states.

21. The method of claim 7 wherein said determined level of  
25 effect of said one or more therapies is a level which minimizes the value of an objective function of the difference between said diagnostic profile and the perturbation response profile extracted from said perturbation response curves for each said determined level  
30 of said one or more therapies.

22. The method of claim 20 or 21 wherein said objective function comprises a sum of the squares of differences of the

diagnostic profile and the perturbation response profile extracted from said perturbation response curves.

23. The method of claim 1 or 7 wherein said subject is a  
5 mammal.

24. The method of claim 23 wherein said subject is a human.

25. The method of claim 1 or 7 wherein said first plurality  
10 of cellular constituents and said second plurality of cellular constituents comprise abundances of a plurality of RNA species present in said cell type.

26. The method of claim 25 wherein the abundances of said  
15 first plurality and said second plurality of RNA species are measured by a method comprising contacting a gene transcript array with RNA from a cell of said cell type, or with cDNA derived therefrom, wherein a gene transcript array comprises a surface with attached nucleic acids or nucleic acid mimics,  
20 said nucleic acids or nucleic acid mimics capable of hybridizing with said plurality of RNA species, or with cDNA derived therefrom.

27. The method of claim 26 wherein said measuring of said  
25 abundances of said second plurality of RNA species is performed by a method comprising contacting one or more gene transcript arrays (i) with RNA, or with cDNA derived therefrom, from said cell of said subject, and (ii) with RNA, or with cDNA derived therefrom, from a second cell of a  
30 second subject not having a disease or undergoing therapy.

28. The method of claim 25 wherein said first plurality of RNA species constitutes the majority of RNA species known to be increased or decreased in said cell in response to

perturbations correlated to said disease state or to said therapy.

29. The method of claim 26 wherein said first plurality of  
5 RNA species constitutes the majority of RNA species known to be increased or decreased in said cell in response to perturbations correlated to said disease state or to said therapy.

10 30. The method of claim 1 or 7 wherein said cellular constituents comprise abundances of a plurality of protein species present in said cell type.

31. The method of claim 30 wherein the abundances of said  
15 plurality of protein species are measured by a method comprising contacting an antibody array with proteins from a cell of said cell type, wherein said antibody array comprises a surface with attached antibodies, said antibodies capable of binding with said plurality of protein species.

20 32. The method of claim 27 wherein the abundances of said plurality of protein species are measured by a method comprising performing two-dimensional electrophoresis of proteins from a cell of said cell type.

25 33. The method of claim 1 or 7 wherein said cellular constituents comprise activities of a plurality of protein species present in said cell type.

30 34. A computer system for determining a level of one or more disease states in a subject comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising determining, for

each of said disease states, an interpolated response profile, from interpolated perturbation response profiles correlated to levels of each of said disease states, for which similarity is greatest between a diagnostic profile and  
5 said one or a combination of said determined interpolated response profiles, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in one or more cells of said subject, and wherein said interpolated response profiles are  
10 the products of a method comprising

(i) providing response profiles of one or more cells of one or more analogous subjects for each of said disease states wherein said response profiles are obtained by measuring a second plurality of  
15 cellular constituents in said cells of said one or more analogous subject at a plurality of levels for each of said disease states, and

(ii) interpolating said response profiles so that a response profile may be extracted over a range of  
20 levels for each of said disease states,

wherein the level of each disease state correlated to each determined interpolated response profile indicates said levels of said disease states.

25 35. A computer system for determining a level of effect of one or more therapies upon a subject comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising determining, for  
30 each of said therapies, an interpolated response profile from interpolated perturbation response profiles correlated to levels of effect of each of said therapies, for which similarity is greatest between a diagnostic profile and said one or a combination of said determined interpolated response

profiles, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in one or more cells of said subject, and wherein said interpolated response profiles are the products  
5 of a method comprising:

- 10 (i) providing response profiles of one or more cells of one or more analogous subjects for each of said therapies wherein said response profiles are obtained by measuring a second plurality of cellular constituents in said cells of said one or more analogous subjects at a plurality of levels of effect for each of said therapies, and  
15 (ii) interpolating said response profiles so that a response profile may be extracted over a range of levels for each of said therapies,

wherein the level of effect of each therapy correlated  
20 to each determined interpolated response profile indicates said levels of effect of said therapies.

36. The computer system of claim 34 or 35 wherein said determining said interpolated response profile is achieved by  
25 a method comprising:

- (a) determining a value of an objective function of the difference between said diagnostic profile and said determined interpolated response profile; and  
30 (b) minimizing said determined value of said objective function.

37. The computer system of claim 34 or 35 wherein said diagnostic profiles and said response curves are made available in said memory.



38. The computer system of claim 37 wherein said programs cause said processor to perform said step of interpolating said response profiles.

5 39. The computer system of claim 36 wherein said objective function comprises a sum of the squares of differences of said diagnostic profile and said determined interpolated response profile.

10 40. The computer system of claim 36 wherein said objective function comprises a negative of a correlation of the diagnostic profile and said determined interpolated response profile extracted from said perturbation response curves.

15 41. The computer system of claim 36 wherein said minimizing comprises performing the Levenberg-Marquandt method.

42. A kit for determining a level of one or more disease states in a subject comprising a solid phase containing on  
20 its surface a plurality of nucleic acids of known, different sequences, each at a known location on said solid phase, each nucleic acid capable of hybridizing to an RNA species or cDNA species derived therefrom, wherein said RNA species are known to be increased or decreased at different levels of said  
25 disease states, said plurality substantially excluding nucleic acids capable of hybridizing to RNA species that are not so increased or decreased.

43. A kit for determining a level of effect of one or more  
30 therapies in a subject comprising a solid phase containing on its surface a plurality of nucleic acids of known, different sequences, each at a known location on said solid phase, each nucleic acid capable of hybridizing to an RNA species or cDNA species derived therefrom, wherein said RNA species are known

to be increased or decreased at different levels of said effect of said therapies, said plurality substantially excluding nucleic acids capable of hybridizing to RNA species that are not so increased or decreased.

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44. A kit for determining a level of one or more disease states in a subject comprising:

10 (a) a solid phase containing on its surface a plurality of nucleic acids of known, different sequences, each at a known location on said solid phase, each nucleic acid capable of hybridizing to an RNA species or cDNA species derived therefrom, wherein said RNA species are known to be increased or decreased at different levels of said disease states, and

15 (b) response profiles, in electronic or written form, correlated to levels of each of said disease states, wherein said response profiles are obtained by measuring a plurality of cellular constituents in a cell or cells of one or more analogous subjects at a plurality of  
20 levels for each of said disease states.

45. A kit for determining a level of effect of one or more therapies in a subject comprising:

25 (a) a solid phase containing on its surface a plurality of nucleic acids of known, different sequences, each at a known location on said solid phase, each nucleic acid capable of hybridizing to an RNA species or cDNA species derived therefrom, wherein said RNA species are known to be increased or decreased at different levels of said effect of therapies, and  
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(b) response profiles, in electronic or written form, correlated to levels of effect of each of said therapies, wherein said response profiles are obtained by measuring a plurality of cellular constituents in a

cell or cells of one or more analogous subjects at a plurality of levels of effect of each of said therapies.

46. The kit of claim 44 or 45 wherein said response profiles  
5 are interpolated.

47. The kit of claim 44 or 45 wherein said perturbation  
response curves are in electronic form, and wherein said kit  
further comprises expression profile analysis software on  
10 computer readable medium, said software capable of being  
encoded in a memory of a computer also having a processor,  
said encoded software causing said processor to perform a  
method comprising:

- 15 (a) receiving a diagnostic profile of a cell of said  
subject, said diagnostic profile having been obtained by  
a method comprising measuring abundances of RNA species  
or cDNA derived therefrom from said cell;
- (b) receiving said response profiles; and
- 20 (c) determining the response profile for each of said  
disease states or therapies for which similarity is  
greatest between said diagnostic profile and a  
combination of said determined interpolated response  
profiles,

wherein the level correlated to each determined response  
25 profile indicates said level of said disease states or of  
said effect of said therapies.

48. A database comprising response profiles for one or more  
disease states or therapies wherein said database is in  
30 electronic form, wherein said response profiles are obtained  
by measuring a plurality of cellular constituents in a cell  
or cells of one or more analogous subjects at a plurality of  
levels for each of said disease states or effects of said  
therapies.

49. The database of claim 48 wherein said response profiles are interpolated.

50. The method of claim 1 wherein the disease is cancer,  
5 hypertension, a neurodegenerative disease, or a neuropsychiatric disorder.

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